A Rationale for the Use of Norepinephrine after the Control of Bleeding in Hemorrhagic Shock?

The fifth edition of the European guidelines on management of major bleeding and coagulopathy after trauma recommends the use of vasopressors in addition to fluids to maintain target arterial pressure (Grade 1C: strong recommendation with low-quality evidence) (1). Conversely, in the U.S. guidelines and most recent review related to hemorrhagic shock management, use of vasopressors is not mentioned (2, 3).

The pathophysiology of hemorrhagic shock is well known; during the early compensatory phase there is a sympathoexcitatory response, which alters to a sympathoinhibitory response when the bleeding becomes severe and/or when anesthetics are administrated to manage the associated trauma. Despite control of the bleeding source and adequate transfusion, some patients experience a persistent hypotensive state associated with capillary leak syndrome and a systemic inflammatory response mirroring a sepsis-like syndrome, which is similar to ischemia–reperfusion–related injury (3–4).

Preclinical studies have demonstrated that the decreases in arterial pressure, cardiac output, and oxygen carrying capacity of the blood induced by hemorrhagic shock activate the sympathetic nervous and renin angiotensin systems. These changes cause a reduction in renal blood flow, renal oxygen delivery, and renal microcirculatory perfusion and oxygenation (5), which likely contribute to the decrease in renal function that develops during hemorrhage. Supporting this notion are the findings that acute kidney injury develops in septic shock, where there are also decreases in renal perfusion and oxygenation (6). Interestingly, such decreases in perfusion and oxygenation are selective to the renal medulla, in accord with the proposition that the renal medulla is susceptible to hypoperfusion and hypoxia.

Fluid resuscitation is the primary treatment for hemorrhage to normalize intravascular volume, preload, and cardiac output with the aim of increasing arterial pressure and oxygen delivery to tissues to improve perfusion and oxygenation. In a series of studies in hemorrhaged anesthetized rats, fluid resuscitation with a range of crystalloid fluids did not restore renal cortical or medullary oxygenation, although arterial pressure and renal blood flow were improved (5); another group found resuscitation with Ringer's lactate partially restored renal perfusion (7). In sepsis, resuscitation with fluid and norepinephrine is the primary treatment, and the detrimental effects of resuscitation with norepinephrine in sepsis have been reported (6). In contrast, the effects of fluid plus norepinephrine resuscitation on renal perfusion and oxygenation during hemorrhage are not well understood, and the use of norepinephrine has been questioned in view of its ability to cause renal vasoconstriction.

In mice with uncontrolled hemorrhagic shock, compared with fluid alone, a combination of fluid plus norepinephrine reduced fluid requirement and blood loss, improved splanchnic microcirculatory blood flow (8), and improved survival (9). In uncontrolled lethal models of hemorrhagic shock, vasopressin, but not resuscitation with crystalloid, significantly improved survival (10). In clinical practice, excluding treatment of patients with traumatic brain injury, the ideal strategy remains unclear. The results of retrospective studies support that the combination of fluid resuscitation with vasopressors is associated with significantly higher mortality (11–13), whereas the prospective studies that tested low doses of vasopressin in young patients with trauma are more positive. Treatment with low doses of vasopressin, randomly added to fluid resuscitation in 78 critically ill patients with trauma with penetrating injuries is associated with reduced fluid requirements (14). More recently, a small randomized controlled trial recruited 100 patients with trauma (most with penetrating injuries) and tested the association of low doses of vasopressin versus fluid alone. Vasopressin was associated with a significantly reduced requirement for blood but not fluids (15). In both these randomized controlled trials, vasopressin treatment did not improve mortality.

In this issue of the *Journal*, Libert and colleagues (pp. 34–43) report the results of an experimental study of controlled hemorrhage in anesthetized pigs with a subcostal lobotomy, which mimics a penetrating injury (16). They studied the effects of treatment with a combination of norepinephrine with fluid versus fluid alone on renal microcirculatory perfusion, renal oxygenation, renal function, and renal histology 48 hours after hemorrhage. The main finding was that the combination of norepinephrine with fluids was as safe as fluid alone and reduced fluid requirements and therefore the degree of hemodilution. Both treatments caused a similar restoration of renal microcirculation and oxygenation in the cortex and medulla, accompanied by increased renal function; neither treatment caused damage to the kidney. This finding contrasts with the situation in sepsis, where resuscitation with norepinephrine worsened the amount of hypoxia in the renal medulla (7), which may be due to the excessive inflammation in that condition. In view of this, as indicated by the authors, a future study of a hemorrhagic model with severe trauma, which would induce an inflammatory response, would be important. The strength of this experimental study is that it studied a large animal model that is likely to be more clinically relevant than rodent models. Furthermore, it is based on a plausible clinical scenario of penetrating trauma with pragmatic outcome assessments (renal function, fluid requirements, renal microcirculatory blood flow, and renal histology at 48 hours) and supports the concept of safe use of norepinephrine once the bleeding source is controlled.

Originally Published in Press as DOI: 10.1164/rccm.202203-0521ED on April 21, 2022

Am J Respir Crit Care Med Vol 206, Iss 1, pp 1–16, Jul 1, 2022
Internet address: www.atsjournals.org

Other limitations to the clinical message are the use of young pigs that are more resistant to hypotension, as suggested by the absence of mortality in this study. The results may be different in older comorbid animals or an older clinical population with chronic hypertension, for instance. This study confirms that in hemorrhagic shock adding norepinephrine to fluid resuscitation does not threaten the renal microcirculation or renal function. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Pierre Asfar, M.D., Ph.D.
Centre Hospitalo-Universitaire d'Angers
Université d'Angers
Angers, France

Clive May, Ph.D.
Florey Institute of Neuroscience and Mental Health
University of Melbourne
Parkville, Victoria, Australia

References

1. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, *et al.* The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care* 2019; 23:98.
2. Cannon JW, Khan MA, Raja AS, Cohen MJ, Como JJ, Cotton BA, *et al.* Damage control resuscitation in patients with severe traumatic hemorrhage: A practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg* 2017; 82:605–617.
3. Cannon JW. Hemorrhagic shock. *N Engl J Med* 2018;378:370–379.
4. Richards JE, Harris T, Dünser MW, Bouzat P, Gauss T. Vasopressors in trauma: a never event? *Anesth Analg* 2021;133:68–79.
5. Ergin B, Akin S, Ince C. Kidney microcirculation as a target for innovative therapies in AKI. *J Clin Med* 2021;10:4041.
6. Lankadeva YR, Kosaka J, Evans RG, Bailey SR, Bellomo R, May CN. Intrarenal and urinary oxygenation during norepinephrine resuscitation in ovine septic acute kidney injury. *Kidney Int* 2016;90:100–108.
7. van Leeuwen ALI, Dekker NAM, Van Slyke P, de Groot E, Vervloet MG, Roelofs JJTH, *et al.* The effect of targeting Tie2 on hemorrhagic shock-induced renal perfusion disturbances in rats. *Intensive Care Med Exp* 2021;9:23.
8. Harrois A, Baudry N, Huet O, Kato H, Dupic L, Lohez M, *et al.* Norepinephrine decreases fluid requirements and blood loss while preserving intestinal villi microcirculation during fluid resuscitation of uncontrolled hemorrhagic shock in mice. *Anesthesiology* 2015;122: 1093–1102.
9. Poloujadoff M-P, Borron SW, Amathieu R, Favret F, Camara MS, Lapostolle F, *et al.* Improved survival after resuscitation with norepinephrine in a murine model of uncontrolled hemorrhagic shock. *Anesthesiology* 2007;107:591–596.
10. Stadlbauer KH, Wagner-Berger HG, Krismer AC, Voelckel WG, Konigsrainer A, Lindner KH, *et al.* Vasopressin improves survival in a porcine model of abdominal vascular injury. *Crit Care* 2007;11:R81.
11. Fangio P, Asehnoune K, Edouard A, Smail N, Benhamou D. Early embolization and vasopressor administration for management of life-threatening hemorrhage from pelvic fracture. *J Trauma* 2005;58: 978–984. [Discussion, p. 984].
12. Sperry JL, Minei JP, Frankel HL, West MA, Harbrecht BG, Moore EE, *et al.* Early use of vasopressors after injury: caution before constriction. *J Trauma* 2008;64:9–14.
13. Plurad DS, Talving P, Lam L, Inaba K, Green D, Demetriades D. Early vasopressor use in critical injury is associated with mortality independent from volume status. *J Trauma* 2011;71:565–570. [Discussion, pp. 570–572].
14. Cohn SM, McCarthy J, Stewart RM, Jonas RB, Dent DL, Michalek JE. Impact of low-dose vasopressin on trauma outcome: prospective randomized study. *World J Surg* 2011;35:430–439.
15. Sims CA, Holena D, Kim P, Pascual J, Smith B, Martin N, *et al.* Effect of low-dose supplementation of arginine vasopressin on need for blood product transfusions in patients with trauma and hemorrhagic shock: a randomized clinical trial. *JAMA Surg* 2019;154:994–1003.
16. Libert N, Laemel E, Harrois A, Laitselart P, Bergis B, Isnard P, *et al.* Renal microcirculation and function in a pig model of hemorrhagic shock resuscitation with norepinephrine. *Am J Respir Crit Care Med* 2022;206:34–43.

Small Airway Anatomy: An Indicator of Pollution Susceptibility in Adults?

It is well accepted that long-term exposure to higher amounts of air pollution impairs lung function in adults and accelerates the rate of lung function decline (1, 2). Ambient pollution exposure may also increase risk of developing chronic obstructive pulmonary disease (COPD), even among never-smokers (3). However, few individual-level traits have been identified that modify the long-term effects of air pollution on adult respiratory health, particularly at low pollutant concentrations just above recently revised World Health Organization air quality guidelines (4). In this issue of the *Journal*, Bourbeau and colleagues (pp. 44–55) sought to address this need (5). The authors evaluated dysanapsis, a mismatch of airway tree caliber to lung parenchyma size, as a potential indicator of pollution susceptibility, building on emerging evidence implicating airway abnormalities and impaired lung growth as risk factors for COPD (6). The authors found that long-term exposure to particulate matter ⩽2.5 μm in aerodynamic diameter ($PM_{2.5}$) and nitrogen dioxide (NO_2) were each associated with lower lung function. Among those in the lowest quartile of radiographic airway-to-lung ratio, the associations of $PM_{2.5}$ with lung function and odds of COPD were greater.

Originally Published in Press as DOI: 10.1164/rccm.202203-0592ED on May 3, 2022